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(71) Applicant: JOHNSON & JOHNSON CONSUMER COMPANIES, INC. [US/US]; 199 Grandview Road, Skillman, NJ 08858 (US).

(72) Inventor: GENDIMENICO, Gerard, J.; 509 Sheppard Court, Neshanic Station, NJ 08853 (US).

(74) Agents: JOHNSON, Philip, S. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).

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(54) Title: COMPOSITIONS CONTAINING A RETINOID AND A STILBENE FOR SKIN CARE

(57) Abstract: The present invention relates to compositions containing a retinoid and a stilbene and the use thereof in skin care (e.g., for the treatment of skin disorders and the lightening of skin).

COMPOSITIONS CONTAINING A RETINOID AND A STILBENE FOR SKIN CARE

FIELD OF THE INVENTION

The present invention relates to compositions containing a retinoid and a stilbene and the use thereof in skin care (e.g., for the treatment of skin disorders and the lightening of skin).

BACKGROUND OF THE INVENTION

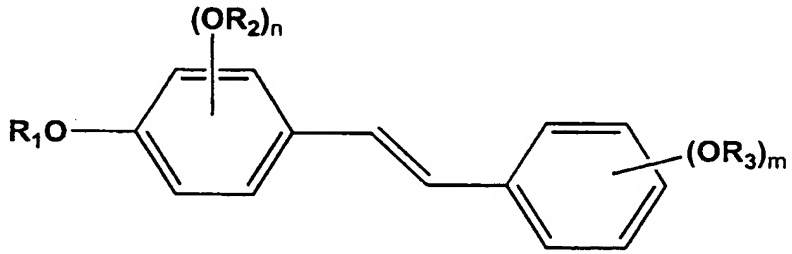
Retinoids are therapeutic agents with wide applications in skin care and treatment, e.g., dermatology (See, Craven NM, Griffiths CE, Topical Retinoids and Cutaneous Biology, *Clin. Exp. Dermatol.* 1996 Jan;21(1):1-10; Futoryan T, Gilchrest BA, Retinoids and the Skin, *Nutr. Rev.* 1994 Sep;52(9):299-310; Torras H, Retinoids in Aging. *Clin. Dermatol.* 1996 Mar-Apr;14(2):207-15; U.S. Patent No. 5,468,495; and U.S. Patent No. 5,051,449). Associated with their topical use, however, is a type of irritation that consists primarily of skin reddening (e.g., erythema). This side effect can be particularly bothersome to subjects, and it can hinder the proper and compliant use of the compounds for their desired benefits. It, therefore, would be advantageous to find a method to enhance the beneficial effects of retinoids (e.g., reduce the amount of retinoid required to be used) without enhancing this side effect that occurs during use.

The present invention relates to a combination of a stilbene and a retinoid. The combination was found to potentiate the biological effectiveness of the retinoid

without a corresponding enhancement of the skin irritation response.

SUMMARY OF THE INVENTION

In one aspect, the invention features a method of treating the skin, said method comprising administering to the skin (e.g., the skin of a mammal such as a human) a composition comprising a retinoid and stilbene. Examples of stilbenes include those of the following formula:



Formula I

wherein R1 and R2, independently, are selected from the group consisting of H and C1-C6 alkyl; m is selected from the numbers 0-5; and n is selected from the numbers 0-4; or a therapeutically acceptable salt thereof. While drawn in the trans configuration, stilbenes of the above Formula I include both the cis- or trans-isoforms.

In one embodiment, the invention features a method of treating a skin condition selected from the group consisting of acne, oily skin, wrinkles, excessive cellulite, excessive pore size, intrinsic skin aging, photoaging, skin cancer, photodamage, keratinization abnormalities, alopecia, dyspigmentation, psoriasis, skin inflammation, wounds, scarring, stretch marks, and skin atrophy. In one embodiment, the invention features a method of lightening the skin.

In one aspect, the invention features a composition, said composition comprising a retinoid and a compound of Formula I wherein R1 and R2, independently, are selected from the group consisting of H and C1-C6 alkyl; m is selected from the numbers 0-5; and n is selected from the numbers 0-4; or a therapeutically acceptable salt thereof.

In one aspect, the invention features a method of enhancing the therapeutic efficacy of a retinoid, said method comprising: applying (e.g., to the skin) a composition containing a stilbene (e.g., from about 0.01 to about 10 percent, by weight of the composition) prior to, during, or after application (e.g., to the skin) of said retinoid.

In one aspect, the invention features a cosmetic composition, said composition comprising a composition of claim 1 and a dermatologically-acceptable topical carrier.

Other features and advantages of the present invention will be apparent from the detailed description of the invention and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

It is believed that one skilled in the art can, based upon the description herein, utilize the present invention to its fullest extent. The following specific embodiments are to be construed as merely illustrative and are not limited by the remainder of the disclosure in any way whatsoever.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art

to which the invention belongs. Also, all publications, patent applications, patents, and other references mentioned herein are incorporated by reference.

The present invention relates to a composition comprising a retinoid and a compound of the Formula I, wherein R1 and R2, independently, are selected from the group consisting of H and C1-C6 alkyl; m is selected from the numbers 0-5; and n is selected from the numbers 0-4; or a therapeutically-acceptable salt thereof.

In one embodiment, all R1 and R2, independently, are selected from H or CH_3. In one embodiment, n and m are independently, selected from 0 and 1. Examples of compounds of the above formula are the cis- or trans-isomers of the stilbenes 3,5,4'-trihydroxystilbene, 3,5-methoxy,3,4-hydroxystilbene, 2,3',4,5'-tetrahydroxystilbene, 3,3'-hydroxy, 4,4'-methoxy-stilbene, 3,3',4,5'-tretrahydroxystilnene,4-hydroxystilbene. Examples of these and other stilbenes, as well as the synthesis of such compounds, are disclosed in Japanese Patent Application Publication No. 2503218 (1996).

What is meant by a stilbene is a stilbene that is optionally substituted with various chemical moieties (e.g., substituted with 1-10 hydroxy or C1-C6 alkoxy groups on the benzyl rings of the stilbene). Examples of stilbenes are the compounds of Formula I.

What is meant by therapeutically acceptable salt is a salt that does not eliminate the therapeutic benefit of the stilbene. Examples of therapeutically acceptable salts are those with therapeutically acceptable organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methesulfonic,

toluenesulfonic, or pamoic acid), as well as polymeric acids (e.g., tannic or carboxymethyl cellulose), and salts with inorganic acids as a hydrohalic acid (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid).

In one embodiment, the retinoid is selected from the group consisting of retinol, retinoic acid, retinal, retinyl palmitate, and retinyl acetate, which includes the sterioisomers thereof (e.g., retinoic acid includes all-trans retinoic acid, 9-cis-retinoic acid, and/or 13-cis-retinoic acid).

The amount of stilbene and retinoid in the composition varies depending on the skin condition being treated, the manner of administration, and the age and body weight of the subject. Such amount is referred to herein as a "therapeutically effective amount." The retinoid and stilbene, independently, will typically be present in the composition in an amount from about 0.001% to about 10% by weight of the composition, e.g., from about 0.001% to about 5% such as from about 0.1% to about 2%.

In one embodiment, the composition further comprises another dermatologically active agent. What is meant by a "dermatologically active agent" is a compound that has a cosmetic or therapeutic effect on the skin. In one embodiment, the agent is selected from the group consisting of hydroxy acids, benzoyl peroxide, sulfur resorcinol, ascorbic acid, D-panthenol, hydroquinone, sunscreen agents, antiinflammatory agents, skin lightening agents, antimicrobial and antifungal agents, estrogens, and derivatives and mixtures thereof. The dermatologically active agent will typically be present in the composition of the invention in an amount of from

about 0.001% to about 20% by weight of the composition, e.g., about 0.01% to about 10%, e.g., about 0.1% to about 5%.

Examples of hydroxy acids include, but are not limited, to (i) alpha-hydroxy acids such as glycolic acid, lactic acid, malic acid, citric acid, and tartaric acid, (ii) beta-hydroxy acids such as salicylic acid, and/or (iii) polyhydroxy acids. See, e.g. European Patent Application No. 273,202.

Examples of derivatives of ascorbic acid include, but are not limited to, ascorbyl palmitate, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, zinc ascorbyl phosphate, ascorbyl glucoside, sodium ascorbate, and ascorbyl polypeptide. An example of a derivative of hydroquinone includes, but is not limited to, arbutin. The composition of the present invention may also comprise one or more of the following: antioxidants (e.g., ascorbic acid, tocopherols, BHA, and BHT), chelating agents (e.g., EDTA), and preservatives (e.g., parabens). Examples of suitable antioxidants, preservatives, and chelating agents are listed in the International Cosmetic Ingredient Dictionary and Handbook, eds. Wenninger and McEwen, pp. 1612-13, 1626, and 1654-55 (The Cosmetic, Toiletry, and Fragrance Assoc., Washington, D.C., 7th Edition, 1997) (hereinafter "ICT Handbook").

The compositions of the present invention can be administered topically to a mammal, e.g., by the direct laying on or spreading of a cosmetic containing the above described composition on the skin of a human. The topical compositions useful in the subject invention involve formulations suitable for topical application to mammalian skin, the formulation comprising a safe and

effective amount of the retinoid, the stilbene, optionally another dermatologically active agent(s), and a dermatologically-acceptable topical carrier. The term "dermatologically-acceptable topical carrier" refers to a carrier for topical use that is capable of having the retinoid and the stilbene dispersed or dissolved therein, and possessing acceptable safety properties.

The topical compositions useful in the present invention may be made into a wide variety of product types. These include, but are not limited to lotions, creams, gels, sticks, sprays, ointments, pastes, mousses, cosmetics and dermal patches. These product types may comprise several types of carrier systems including, but not limited to solutions, emulsions, gels, solids, and liposomes.

The topical compositions useful in the present invention formulated as solutions typically include a dermatologically-acceptable aqueous and/or organic carriers (e.g., from about 80% to about 99.99 or from about 90% to about 99% %, by weight of the composition, of an acceptable aqueous or organic solvent). Examples of suitable organic solvents include: propylene glycol, polyethylene glycol (200-600), polypropylene glycol (425-2025), glycerol, 1,2,4-butanetriol, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, butanetriol, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, butanediol, and mixtures thereof.

If the topical solution useful in the present invention are formulated as an aerosol and applied to the skin as a spray-on, a propellant is added to a solution composition. Examples of propellants useful herein include, but are not limited to, chlorinated, fluorinated,

and chloro-fluorinated lower molecular weight hydrocarbons. Other propellants useful herein can be found in Sagafin, Cosmetics Science and Technology, 2nd Edition, Vol. 2, pp. 443-65 (1972) and the ICT Handbook pp. 1655.

Topical compositions useful in the subject invention may be formulated as a solution comprising an emollient. Such compositions generally contain from about 1% to about 50% by weight of the composition, e.g., from about 5% to about 25%, of a topical dermatologically-acceptable emollient(s). As used herein, "emollients" refer to materials used for the prevention or relief of dryness, as well as for the protection of the skin. A wide variety of suitable emollients are known and may be used herein. Sagafin, *Cosmetics, Science and Technology*, 2nd Edition, Vol. 1, pp. 32-43 (1972) and the ICT Handbook, pp. 1656-61 contains numerous examples of suitable materials.

A lotion can be made from a solution carrier system. Lotions typically comprise from about 1% to about 20% by weight of the composition (e.g., from about 5% to about 10%) of an emollient(s) and from about 50% to about 90% by weight of the composition (e.g., from about 60% to about 80%) of water.

Another type of product that may be formulated from a solution carrier system is a cream. A cream typically comprises from about 5% to about 50% by weight of the composition (e.g., from about 10% to about 20%) of an emollient(s) and from about 45% to about 85% by weight of the composition (e.g., from about 50% to about 75%) of water.

Yet another type of product that may be formulated from a solution carrier system is an ointment. An ointment may comprise a simple base of animal or vegetable oils or semi-solid hydrocarbons. Ointments may also comprise absorption ointment bases that absorb water to form emulsions. Ointment carriers may also be water-soluble. An ointment may comprise from about 1% to about 20% by weight of the composition of an emollient(s) plus from about 0.1% to about 2% by weight of the composition of a thickening agent(s). A more complete disclosure of thickening agents or viscosity increasing agents useful herein can be found in Sagarin, *Cosmetics, Science and Technology*, 2nd Edition, Vol. 1, pp. 72-73 (1972) and the ICT handbook pp. 1693-97.

If the carrier is formulated as an emulsion, from about 1% to about 10% by weight of the composition (e.g., from about 2% to about 5%) of the carrier system may comprise an emulsifier(s). Emulsifiers may be nonionic, anionic, cationic, or zwitterionic. Suitable emulsifiers are disclosed in, for example, U.S. Patent No. 3,755,560, U.S. Patent No. 4,421,769, McCutcheon's Detergents and Emulsifiers, North American Edition, pp. 317-24 (1986), and the ICT Handbook, pp.1673-86.

Lotions and creams can be formulated as emulsions as well as solutions. Typically, lotions may comprise from 0.5% to about 5% by weight of the composition of an emulsifier(s). Creams may typically comprise from about 1% to about 20% by weight of the composition (e.g., from about 5% to about 10%) of an emollient(s); from about 20% to about 80% by weight of the composition (e.g., from 30% to about 70%) of water; and from about 1% to about 10% by

weight of the composition (e.g., from about 2% to about 5%) of an emulsifier(s).

Single emulsion skin care preparations, such as lotions and creams, of the oil-in-water type and water-in-oil type are well-known in the cosmetic art and are useful in the subject invention. Multiphase emulsion compositions, such as the water-in-oil-in-water type, as disclosed in U.S. Patent No. 4,254,105, are also useful in the subject invention. In general, such single or multiphase emulsions contain water, emollients, and emulsifiers as essential ingredients. Triple emulsion carrier systems comprising an oil-in-water-in-silicone fluid emulsion composition as disclosed in U.S. Patent No. 4,960,764 may also be useful in the subject invention.

Another emulsion carrier system useful in the topical compositions is a micro-emulsion carrier system. Such a system may comprise from about 9% to about 15% by weight of the composition of squalane; from about 25% to about 40% by weight of the composition of silicone oil(s); from about 8% to about 20% by weight of the composition of a fatty alcohol(s); from about 15% to about 30% by weight of the composition of polyoxyethylene sorbitan mono-fatty acid(s) (commercially available under the trade name Tweens) or other nonionics; and from about 7% to about 20% by weight of the composition of water.

Liposomal formulations are also useful compositions of the subject invention. Such compositions can be prepared by first combining hesperetin with a phospholipid, such as dipalmitoylphosphatidyl choline, cholesterol and water according to the method described in Mezei & Gulasekharam, "Liposomes--A Selective Drug

Delivery System for the Topical Route of Administration; Gel Dosage Form", *Journal of Pharmaceutics and Pharmacology*, Vol. 34 (1982), pp. 473-74, or a modification thereof. Epidermal lipids of suitable composition for forming liposomes may be substituted for the phospholipid. The liposome preparation may then incorporated into one of the above topical carrier systems (e.g., a gel or an oil-in-water emulsion) in order to produce the liposomal formulation. Other compositions and pharmaceutical uses of topically applied liposomes are described in Mezei, M., "Liposomes as a Skin Drug Delivery System", *Topics in Pharmaceutical Sciences* (D. D. Breimer and P. Speiser, eds.,), Elsevier Science Publishers B. V., New York, N.Y., 1985, pp. 345-58.

If the topical compositions useful in the subject invention are formulated as a gel or a cosmetic stick, such compositions can be formulated by the addition of a suitable amount of a thickening agent, as disclosed supra, to a cream or lotion formulation.

The topical compositions useful in the subject invention may contain, in addition to the aforementioned components, a wide variety of additional oil-soluble materials and/or water-soluble materials conventionally used in topical compositions, at their art-established levels. Various water-soluble materials may also be present in the compositions useful in the subject invention. These include humectants, proteins and polypeptides, preservatives and an alkaline agent. Examples of such agents are disclosed in the ICT Handbook, pp.1650-67. In addition, the topical compositions useful herein can contain conventional

cosmetic adjuvants, such as dyes, opacifiers (e.g., titanium dioxide), pigments and perfumes.

The composition and formulations containing such compositions of the present invention may be prepared using methodology that is well known by an artisan of ordinary skill. The following is a description of the biological testing of a composition of the present invention.

Example 1: Increase of Epidermal Thickness

The ear skin of Abyssinian X Short Hair guinea pigs (Kuiper Rabbit Ranch, Gary, IN) was topically treated once daily for five consecutive days per week for eight weeks. On each animal, one ear was treated with test agent(s), as indicated below in Table 1, and the opposite ear was treated with an ethanol/propylene glycol vehicle. The ears were removed, photographed, and then stored in formalin. Histological sections were prepared and mounted on slides. The thickness of the epidermis was measured using computer-aided image analysis. Four areas of each section of the epidermis of each animal were quantified. The following results were obtained:

Table 1

Treatment (Dose, as % w/v)	% Increase in Epidermal Area over Vehicle*
Retinol (0.01%)**	41.8
3,5,4'-Trihydroxystilbene (1%)***	35.2
Retinol (0.01%) plus 3,5,4'-Trihydroxystilbene (1%)	145.6

* % Increase in Epidermal Area over Vehicle = (Agent(s) treated area - Vehicle treated area)/(Vehicle treated area) x 100%

** retinol was obtained from BASF, Mount Olive, NJ

*** 3,5,4'-Trihydroxystilbene was obtained from Sigma Chemical Co., St. Louis, MO

The increase in the thickness of the epidermis was surprisingly found to be much more than additive when both retinol and 3,5,4'-trihydroxystilbene are applied to the skin.

The above assay is a test that is often used to determine retinoid activity (See, Connor MJ, et al., A Comparative Study of the Induction of Epidermal Hyperplasia by Natural and Synthetic Retinoids. *J. Pharmacol. Exp. Ther.* 1986 Apr;237(1):31-35). Thus, 3,5,4'-trihydroxystilbene is a strong potentiator of retinoid activity, and, thus, can be used to enhance retinoids ability to both treat and prevent the following skin conditions: acne, oily skin, wrinkles, excessive cellulite, excessive pore size, intrinsic skin aging, photoaging, skin cancer, photodamage, keratinization abnormalities, alopecia, dyspigmentation, psoriasis, skin inflammation, wounds, scarring, stretch marks and skin atrophy.

Example 2- Depigmentation of Skin

The sections of skin removed from the animals in Example 1 were then stained by the Fontana-Masson technique (See *Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology*, 3rd edition, L.G. Luna (ed.), McGraw-Hill, NY, 1968, pp. 104-105 and

supplies from Poly Scientific, Bay Shore, NY) so that melanin in the skin was visualized and could be quantified by computer-aided image analysis. The percent area of epidermis occupied by melanin was then calculated for each treatment group. Normally the skin epidermal melanin content in these guinea pigs is 10% or greater.

Treatment (Dose, as % w/v)	Percent of animals having ears with visibly observed skin lightening*	Percent of animals having an epidermal melanin content less than 10%*
Vehicles	0	0
Retinol (0.01%)	0	33%
3,5,4'-Trihydroxystilbene (1%)	33%	33%
Retinol (0.01%) plus 3,5,4'-Trihydroxystilbene (1%)	100%	100%

*(n=3 for each of the three treatment group; n=9 for Vehicles)

As shown in the above table, the depigmenting activity of the combination of retinol and 3,5,4'-trihydroxystilbene was surprisingly found to be far superior to either retinol or 3,5,4'-trihydroxystilbene alone. In contrast to treatment with single agents, all animals treated with combination had visibly apparent depigmentation of the skin and a reduction in melanin content to below 10%.

Example 3 - Skin Irritation

The fur of New Zealand White rabbits (Charles River, Wilmington, MA) was clipped at four sites. Test materials were topically applied twice daily to each of the four sites, five consecutive days the first week and then four consecutive days in the second week. Sites were visually scored for the degree of erythema (1 = minimal, 2 = moderate, 3=severe) 24 hours after the final dosing, which was on the fifth day of the second week..

Treatment (Dose, as % w/v)	Erythema Irritation Score(0-3 scale)
Vehicle (ethanol/propylene glycol)	0
Retinol (0.3%)	1.8
3,5,4'-Trihydroxystilbene (1%)	0
Retinol (0.3%) plus 3,5,4'-Trihydroxystilbene (1%)	1.8

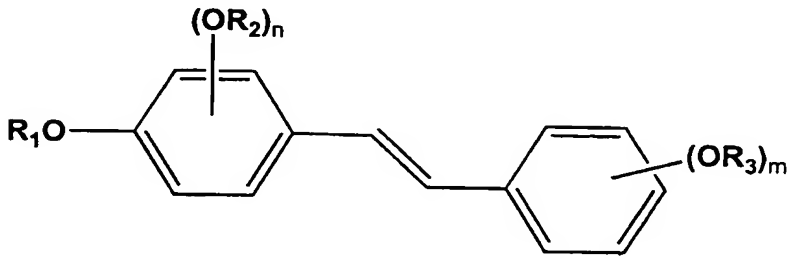
As expected, retinol caused a marked irritation response. The vehicle or trihydroxystilbene alone did not produce any visible irritation. An identical degree of irritation was observed with the combination of retinol and 3,5,4'-trihydroxystilbene. This demonstrates that stilbene compounds potentiate only the useful or beneficial retinoid activities (e.g., as seen in Example 1 and 2) and not the bothersome side effects of skin irritation (skin reddening).

It is understood that while the invention has been described in conjunction with the detailed description thereof, that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims.

Other aspects, advantages, and modifications are within the claims.

What is claimed is:

1. A method of treating the skin, said method comprising administering to the skin a composition, said composition comprising a retinoid and a compound of the formula:



wherein R1 and R2, independently, are selected from the group consisting of H and C1-C6 alkyl; m is selected from the numbers 0-5; and n is selected from the numbers 0-4; or a therapeutically acceptable salt thereof.

2. A method of claim 1, wherein said method comprises treating a skin condition selected from the group consisting of acne, oily skin, wrinkles, excessive cellulite, excessive pore size, intrinsic skin aging, photoaging, skin cancer, photodamage, keratinization abnormalities, alopecia, dyspigmentation, psoriasis, skin inflammation, wounds, scarring, stretch marks and skin atrophy.

3. A method of claim 1, wherein said retinoid is selected from the group consisting of retinoic acid, retinal, retinyl palmitate, and retinyl acetate.

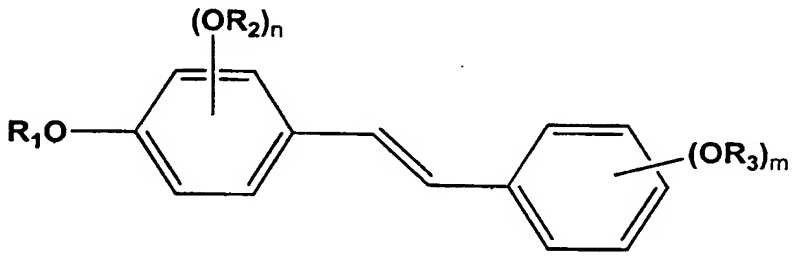
4. A method of claim 1, wherein said retinoid is retinol.

5. A method of claim 1, wherein said R1 and R2 are H.

6. A method of claim 1 comprising the compound 3,5,4'-trihydroxystilbene.

7. A method of claim 4 comprising the compound 3,5,4'-trihydroxystilbene.

8. A method of lightening the skin, said method comprising administering to the skin a composition, said composition comprising a retinoid and a compound of the formula:



wherein R1 and R2, independently, are selected from the group consisting of H and C1-C6 alkyl; m is selected from the numbers 0 - 5; and n is selected from the numbers 0 - 4; or a therapeutically acceptable salt thereof.

9. A method of claim 8, wherein said method comprises treating a skin condition selected from the group consisting of acne, oily skin, wrinkles, excessive cellulite, excessive pore size, intrinsic skin aging,

photoaging, skin cancer, photodamage, keratinization abnormalities, alopecia, dyspigmentation, psoriasis, skin inflammation, wounds, scarring, stretch marks and skin atrophy.

10. A method of claim 8, wherein said retinoid is selected from the group consisting of retinoic acid, retinal, retinyl palmitate, and retinyl acetate.

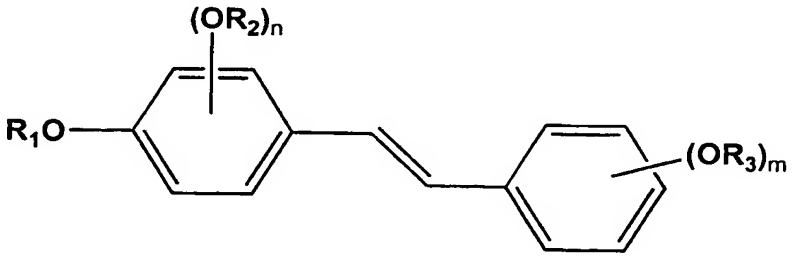
11. A method of claim 8, wherein said retinoid is retinol.

12. A method of claim 8, wherein said R1 and R2 are H.

13. A method of claim 8 comprising the compound 3,5,4'-trihydroxystilbene.

14. A method of claim 8 comprising the compound 3,5,4'-trihydroxystilbene.

15. A composition, said composition comprising a retinoid and a compound of the formula:



wherein R1 and R2, independently, are selected from the group consisting of H and C1-C6 alkyl; m is selected from

the numbers 0 -5; and n is selected from the numbers 0 - 4; or a therapeutically acceptable salt thereof.

16. A composition of claim 15, wherein said retinoid is selected from the group consisting of retinoic acid, retinal, retinyl palmitate, and retinyl acetate.

17. A composition of claim 15, wherein said retinoid is retinol.

18. A composition of claim 15, wherein said R1 and R2 are H.

19. A composition of claim 15 comprising the compound 3,5,4'-trihydroxystilbene.

20. A composition of claim 17 comprising the compound 3,5,4'-trihydroxystilbene.

21. A topical cosmetic composition, said composition comprising a composition of claim 15 and a dermatologically-acceptable topical carrier.